REMARKS

In response to the Office Action mailed February 27, 2006 Applicants respectfully request reconsideration. Claims 1-6 and 10-29 were last presented for examination in this application. All claims were rejected in the outstanding office action. By the foregoing amendments, Claim 25 has been amended to correct a grammatical error and no claims have been added. Of these claims, there is one independent claim, claim 1. Based on the following remarks, Applicants respectfully request that all outstanding rejections be reconsidered, and that they be withdrawn.

Rejections under 35 U.S.C. § 103 should be withdrawn.

Claims 1-4, 6, and 10-29 stand rejected as allegedly being obvious over Lockhart *et al.* (US Patent No. 6,040,138) (hereinafter "Lockhart), in view of Pharmacia Biotech (Molecular and Cell Biology Product Catalog, 1994) (hereinafter "Pharmacia"), and Williams *et al.* (Nucleic Acids Research, Vol. 22, pages 1365-1367, 1994) (hereinafter "Williams"), and further in view of Stahl *et al.* (The Journal of Histochemistry and Cytology, Vol. 41, pages 1735-1740, 1993) (hereinafter "Stahl"). This rejection is respectfully traversed for the following reasons.

With respect to independent claim 1, the rejection is traversed since the Office Action failed to establish a *prima facie* case of obviousness. The Office Action failed to show that the cited prior art references teach or suggest, either alone or in combination, all the elements of the claims and the Office Action failed to provide a motivation to combine the references.

Claim 1 is directed to a method for detecting different isoforms of RNA by amplification of the RNA using random primers to make cDNA, degradation of the RNA,

fragmentation of the cDNA, labeling of the cDNA fragments, hybridization of the cDNA fragments to an array with isoform specific probes and analysis of the hybridization pattern to detect the presence or absence of hybridization.

A *prima facie* case of obviousness requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure.

MPEP at §2142. These requirements of a *prima facie* case of obviousness are not met for the rejections under 35 U.S.C. §103.

To properly reject a claim under 103 a *prima facie* case of obviousness needs to establish that the references, either alone or in combination teach every claim element. (*See*, MPEP §§ 706.02(j) & 2143). With respect to independent claim 1, the Office Action failed to show that Lockhart, Pharmacia, Williams, and Stahl, either alone of in combination, teach the feature of "degrading the RNA population" or "fragmenting cDNA." The Office Action has not cited any portion of Lockhart, Pharmacia, Williams, or Stahl for teaching "degrading the RNA population" or "fragmenting cDNA." as claimed by claim 1. Williams is cited for the purpose of suggesting that fragmentation would be advantageous, but the Examiner has not pointed to any portion of Williams that teaches fragmentation of cDNA. Therefore, the Office Action has failed to establish a *prima facie* case of obviousness and the rejection of independent claims 1 and dependent claims 2-4, 6, and 10-29.

The Examiner also failed to clearly articulate a suggestion or motivation to combine the references and thus failed to establish a *prima facie* case of obviousness. The Examiner has the initial burden to provide some suggestion of the desirability of combining the references as claimed. "Either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). *See*, MPEP §2142.

The Examiner's line of reasoning supporting a motivation to combine Lockhart and Williams appears to be that, because Williams suggests that dangling ends of a duplex formed by the hybridization of two oligonucleotides have unpredictable effects on the stability of the duplex, that one of skill in the art would be motivated to fragment cDNA prior to hybridization to an array in order to minimize overhangs to increase consistency. Applicants do not find this line of reasoning supported by the teachings of the references.

First, Williams does not teach or suggest methods of fragmenting cDNA. At best Williams teaches that overhangs may have an impact on duplex stability. Second, none of the methods taught in the specification for fragmenting the cDNA would be expected to produce fragments that would eliminate overhangs as the Examiner suggest Williams suggests. The only way to achieve duplexes with no overhang would be to fragment the cDNA to generate fragments that are the exact length of the probes and the exact complement of the probes. It would not be sufficient, as the Examiner suggests, to generate a population of fragments that are a mixture of fragments that are the same size

or smaller than the probes of the array. Smaller fragments would result in an overhang of the probe sequence and would thus result in the same unpredictable effect on duplex stability suggested by the Examiner. Fragments that are not the exact complement of the probe will also generate overhangs. None of the fragmentation methods suggested by the Examiner (DNase I or mechanical fragmenting) would be expected to generate fragments that are both the same size as the probes and also the perfect complement of the probes. There is also no suggestion or teaching in Williams that would lead one of skill in the art to conclude that the destabilization observed for one 2 base overhang in the context of a duplex of less than 10 base pairs would be generally applicable to hybridization of a complex sample to an array of probes as taught by Lockhart.

Applicants do not believe that the Examiner has made a convincing case that one of skill in the art would be motivated to modify Lockhart by fragmenting the cDNA prior to hybridization on the basis of the teachings of Williams. The Office Action fails to cite any passage of Lockhart that would motivate one of ordinary skill in the art to combine the teachings of Lockhart with Williams. Therefore, without proper objective evidence the Office Action failed to establish a *prima facie* case of obviousness. The Office Action failed to show that the cited prior art references teach or suggest, either alone or in combination, all the elements of the claims and the Office Action failed to provide a motivation to combine the references.

Claim 5 is rejected under 35 U.S.C. §103(a) over Lockhart in view of Pharmacia, Williams, Stahl and further in view of the Gibco BRL Catalog. The Gibco BRL Catalog is cited by the Examiner as teaching the use of terminal transferase for labeling DNA.

Claim 5 is nonobvious for at least the same reasons as stated above for claim 1 from which claim 5 depends.

CONCLUSION

In view of the foregoing, this application should be in condition for allowance. A notice to this effect is respectfully requested.

Dated: June 27, 2005

Respectfully submitted,

/Sandra E. Wells/
Sandra E. Wells
Reg. No. 52,349

Customer No.: 22886
Legal Department
Affymetrix, Inc.
3420 Central Expressway
Santa Clara, CA 95051
Tel: 408/731-5000
Fax: 408/731-5392